



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 277/22, 313/00, 493/02	A1	(11) International Publication Number: WO 99/54318 (43) International Publication Date: 28 October 1999 (28.10.99)
(21) International Application Number: PCT/US99/07448 (22) International Filing Date: 5 April 1999 (05.04.99) (30) Priority Data: 60/082,564 21 April 1998 (21.04.98) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: VITE, Gregory, D.; 28 Continental Lane, Titusville, NJ 08560 (US). KIM, Soong-Hoon, Kim; 13126 East Run Drive, Lawrenceville, NJ 08648 (US). HOFLE, Gerhard; Alter Weg 12a, D-38124 Braunschweig (DE). (74) Agents: HOFFMAN, Frank, P. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: 12,13-CYCLOPROPANE EPOTHILONE DERIVATIVES (57) Abstract The present invention relates to 12,13-position modified epothilone derivatives, methods of preparation of the derivatives and intermediates therefor.		

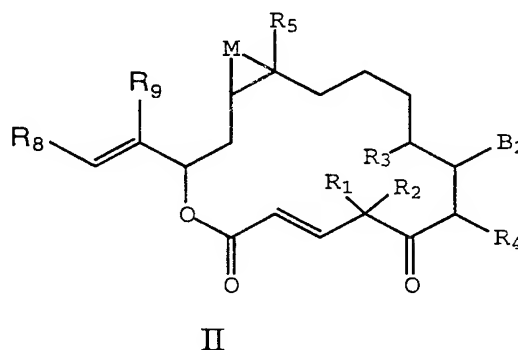
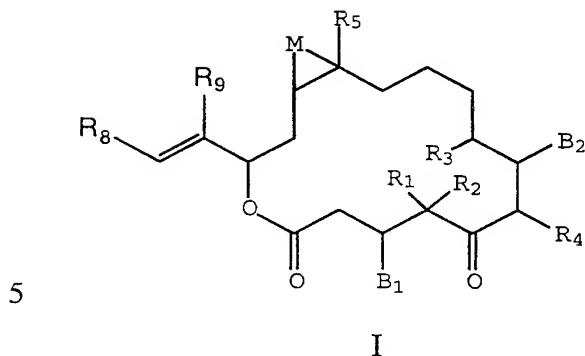
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12,13-CYCLOPROPANE EPOTHILONE DERIVATIVES

The present invention relates to compounds of the formula



B₁ and B₂ are selected from the group consisting of H, or OR₆;

10 R₁, R₂, R₃, and R₄, are selected from H, lower alkyl;

R₅ is selected from the group consisting of H, alkyl, substituted alkyl;

R₈ is heterocyclo;

R₉ is hydrogen or lower alkyl;

15 R₆, is hydrogen or alkyl;

M is CR₁₀R₁₁.

R₁₀ and R₁₁ are selected from the group consisting of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo,

20 R₁₂C=O, R₁₃OC=O, R₁₄NHC=O, hydroxy, O-alkyl or O-substituted alkyl, NR₁₅R₁₆;

R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₈ and R₁₉ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, acyl or substituted aryl.

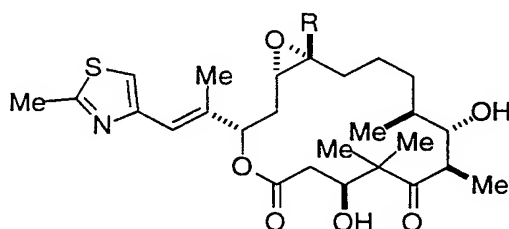
R₁₆ is selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, R₁₇C=O, R₁₈OC=O, R₁₉SO₂, hydroxy, O-alkyl, or O-substituted alkyl and any salts, solvates or hydrates thereof.

5

Background of the Invention

Epothilones are macrolide compounds which find utility in the pharmaceutical field. For example, Epothilones A and B having the structures:

10



Epothilone A R = H

Epothilone B R = Me

15 have been found to exert microtubule-stabilizing effects similar to TAXOL and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease, see Angew. Chem. Int. Ed. Engl., 1996, 35, No. 13/14.

20

Detailed Description of the Invention

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

25

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

5 The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, phenyl, substituted phenyl, heterocyclo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkoxy, heterocycloxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, 10 disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, 15 arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g. CONH_2), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, 20 such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

25 The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocycloxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "cycloalkyl" refers to optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms

may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclos, such as, epoxides and aziridines.

5 The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

 The compounds of formula I and II may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as
10 arginine, lysine and the like. Such salts can be obtained, for example, by exchanging the carboxylic acid protons, if they contain a carboxylic acid, in compounds of formula I and II with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by evaporation. Other salts can be formed as known to those skilled in the art.

15 The compounds for formula I and II form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, hydroxyethanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others
20 (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts are formed by reacting a compound of formula I and II in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

25 In addition, zwitterions ("inner salts") are formed.

 Compounds of the formula I and II may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent

(i.e., the compound for formula I and II) is a prodrug within the scope and spirit of the invention.

For example compounds of the formula I and II may form a carboxylate ester moiety. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s).

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and
10 Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991);
- 15 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Phar Bull, 32, 692 (1984).

20 It should further be understood that solvates (e.g., hydrates) of the compounds of formula I and II are also within the scope of the present invention. Methods of solvation are generally known in the art.

Use and Utility

25

The compounds of formula I and II are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers, including (but not limited to) the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- 10 - tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- 15 - tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
- other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.
- 20

Compounds of formula I and II may also inhibit tumor angiogenesis, thereby affecting the growth of tumors. Such anti-angiogenesis properties of the compounds of formula I and II may also be useful in the treatment of certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

25

Compounds of formula I and II may induce or inhibit apoptosis, a physiological cell death process critical for normal development and

homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of formula I and II, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer

5 (particularly, but not limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases

10 (including but not limited to systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral

15 sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including but not limited to chronic

20 anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

The compounds of this invention are also useful in combination with

25 known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage

range. Compounds of formula I and II can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different
5 phase of the cell cycle, e.g. S phase, than the present compounds of formula I and II which exert their effects at the G₂-M phase.

The present compounds may exist as multiple optical, geometric, and stereoisomers. Included within the present invention are all such isomers and mixtures thereof in the racemic form.

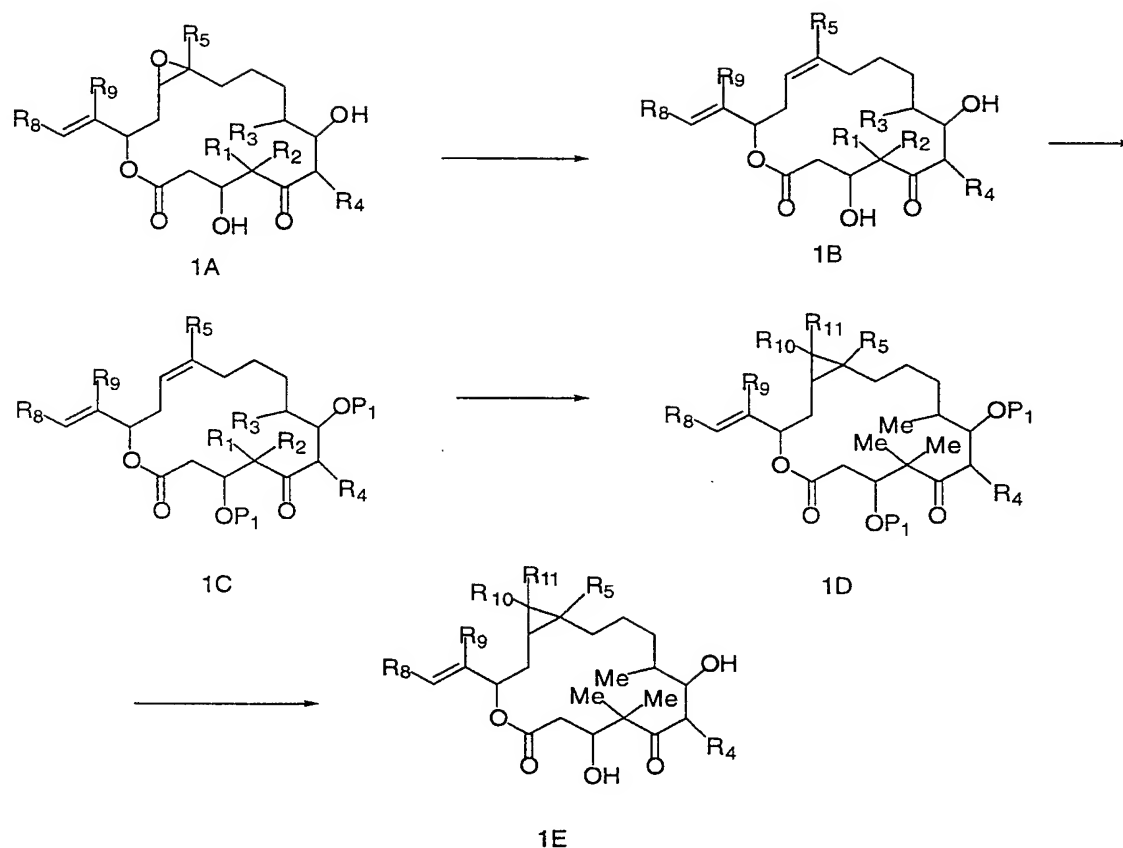
10 The compounds of this invention can be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds
15 can be administered in the form of tablets, capsules, granules, powders and the like. The compounds are administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

20

Methods of Preparation

Compounds of formula I and II are prepared by the following schemes.

25

Scheme 1

5

Compounds of formula I can be prepared as outlined in Scheme 1.

A compound of formula 1B can be prepared from an epothilone of formula 1A by reduction with a reducing agent such as "reactive titanocene" (Cp₂TiCl₂/Mg) or tungsten metal (WCl₆/n-BuLi). Optionally, a compound of
 10 formula 1C, where P₁ is an oxygen protecting group such as triethylsilyl, can be prepared from a compound of formula 1B by methods known in the art. A compound of formula 1D, where R₁₀ and R₁₁ are H, can be prepared from a compound of formula 1C by addition of a carbene group according to the method of Denmark (Denmark, S. E., et al., *J. Org. Chem.*, (1991) 56,
 15 6974). When P₁ is an oxygen protecting group, a deprotection step using,

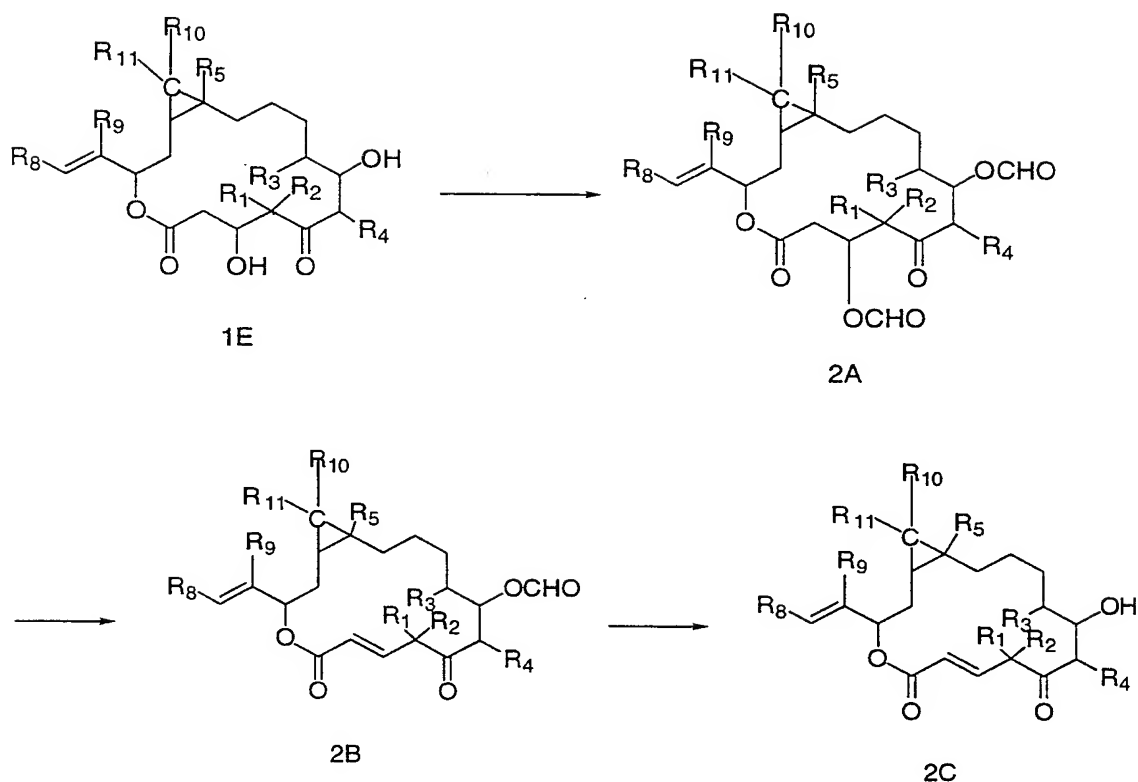
for example when P₁ is a triethylsilyl group, hydrogen fluoride in acetonitrile or tetra-n-butylammonium fluoride in THF or trifluoroacetic acid in dichloromethane provides a compound of formula I (1E) where R₁, R₂, R₃, R₄ and R₅ are defined as described above.

5 Alternatively, a compound of formula 1B can be converted directly to a compound of formula I (1E) without using oxygen protecting groups (i.e., P₁ is H) using the method described above for the conversion of 1C to 1D.

 Alternatively, a compound of formula 1B, or its optionally protected form 1C, can be converted to a compound of formula 1D where where R₁₀
10 and R₁₁ are halogen, such as bromine, by treatment with a dihalocarbene which can be generated, for example, by reaction of sodium hydroxide and bromoform. Dehalogenation of a compound of formula 1D can be achieved with a reducing agent such as tri-n-butyltin hydride to give a compound of formula I (1E). If P₁ is an oxygen protecting group, a deprotection step
15 using, for example when P₁ is a triethylsilyl group, hydrogen fluoride in acetonitrile or tetra-n-butylammonium fluoride in THF or trifluoroacetic acid in dichloromethane provides a compound of formula I (1E) where R₁, R₂, R₃, R₄ and R₅ are defined as described above.

 Other compounds of formula I (i.e., 1E where R₁₀ and R₁₁ are not H or
20 halo) can be prepared from a compound of formula 1C by reaction of a diazo compound and a transition metal catalyst (See for example: Davies, H.M.L., et al., J. Org. Chem., (1991) 56, 3817, and the methods described in "The Chemistry of the Cyclopropyl Group" Parts 1 and 2, Z. Rappoport, Ed., John Wiley and Sons: New York (1987)).

25

Scheme 2

5

Compounds of formula II can be prepared from a compound of formula IE, where B1 and B2 are hydroxyl groups, as shown in Scheme 2. A compound of formula 2A can be prepared from compounds of formula I by addition of formyl groups using standard conditions such as formic acid, triethylamine, acetic anhydride in dichloromethane. Elimination of a compound of formula 2A using 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane provides a compound of formula 2B. Deprotection of a

compound of formula 2B using ammonia in methanol provides a compound of formula II (2C).

The *in vitro* assessment of biological activity of the compounds of
5 Formula I and II was performed as follows:

In vitro Tubulin Polymerization

Twice cycled (2X) calf brain tubulin was prepared following the procedure of Williams and Lee (see Williams, R.C., Jr., and Lee, J. C. Preparation of tubulin from brain. Methods in Enzymology 85, Pt. D: 376-
10 385, 1982) and stored in liquid nitrogen before use. Quantification of tubulin polymerization potency is accomplished following a modified procedure of Swindell, et al., (see Swindell, C.S., Krauss, N.E., Horwitz, S.B., and Ringel, I. Biologically active taxol analogues with deleted A-ring side chain substituents and variable C-2' configurations. J. Med. Chem.
15 34: 1176-1184, 1991). These modifications, in part, result in the expression of tubulin polymerization potency as an effective concentration for any given compound. For this method, different concentrations of compound in polymerization buffer (0.1M MES, 1mM EGTA, 0.5 mM MgCl₂, pH 6.6) are added to tubulin in polymerization buffer at 37° in
20 microcuvette wells of a Beckman (Beckman Instruments) Model DU 7400 UV spectrophotometer. A final microtubule protein concentration of 1.0 mg/ml and compound concentration of generally 2.5, 5.0, and 10 μM are used. Initial slopes of OD change measured every 10 seconds were calculated by the program accompanying the instrument after initial and
25 final times of the linear region encompassing at least 3 time points were manually defined. Under these conditions linear variances were generally <10⁻⁶, slopes ranged from 0.03 to 0.002 absorbance unit/minute, and maximum absorbance was 0.15 absorbance units. Effective concentration

(EC_{0.01}) is defined as the interpolated concentration capable of inducing an initial slope of 0.01 OD/minute rate and is calculated using the formula:

EC_{0.01} = concentration/slope. EC_{0.01} values are expressed as the mean with standard deviation obtained from 3 different concentrations. EC_{0.01} values

5 for the compounds in this invention fall in the range 0.01-1000 µM.

Cytotoxicity (In-Vitro)

Cytotoxicity was assessed in HCT-116 human colon carcinoma cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay as reported in T.L. Riss, et.

10 al., "Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays," *Mol. Biol. Cell* 3

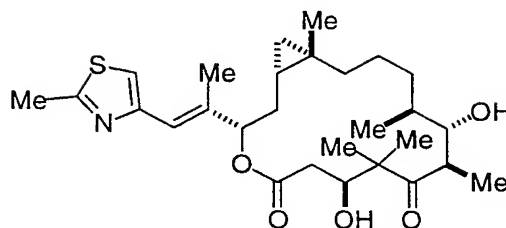
(Suppl.):184a, 1992. Cells were plated at 4,000 cell/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted.

The cells were incubated at 37° for 72 hours at which time the

15 tetrazolium dye, MTS at 333 µg/ml (final concentration), in combination with the electron coupling agent phenazine methosulfate at 25 µM (final concentration) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492nm which can be quantitated spectrophotometrically. The greater the absorbance the greater the

20 number of live cells. The results are expressed as an IC₅₀, which is the drug concentration required to inhibit cell proliferation (i.e. absorbance at 450nm) to 50% of that of untreated control cells. The IC₅₀ values for compounds of this invention fall in the range 0.01 - 1000 nM.

The following examples illustrate the present invention.

Example 1

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

- 10 A. [4S-[4R*,7S*,8R*,9R*,16R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone D]

To anhydrous THF (5 ml) at -78 °C under argon was added WCl_6 (198 mg, 0.5 mmol) followed by $n\text{BuLi}$ (0.625 ml of 1.6 M solution in hexanes, 1.0 mmol). The reaction was allowed to warm to room temperature over a 20 min period. An aliquot (0.50 ml, 0.05 mmol) of the tungsten reagent was removed and added to epothilone B (9.0 mg, 0.018 mmol) under argon and the reaction stirred for 15 min then quenched by the addition of saturated NaHCO_3 (1 ml). The reaction was extracted with EtOAc (3 x 1 ml). The combined extracts dried (Na_2SO_4), and filtered. The volatiles removed under vacuum. The residue was chromatographed with 35% EtOAc/hexanes to give compound A (7.0 mg, 0.014 mmol) in 80% yield. m/z : 492.3 ($\text{M}+\text{H}$)⁺.

20

B. [4S-[4R*,7S*,8R*,9R*,16R*(E)]]-4,8-Bistriethylsilyloxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Bis-Triethylsilyl Epothilone D]

To a solution of compound A (30 mg, 0.061 mmol) in anhydrous
5 CH₂Cl₂ (1.25 mL) under argon were added *N,N*-diisopropylethylamine
(0.16 mL, 0.92 mmol, 15 eq) followed by triethylsilylchloride (0.10 mL, 0.61
mL, 10 eq). The reaction mixture was stirred for 18 hrs. The reaction
mixture was cooled to 0 °C then 2,6-lutidine (0.021 mL, 0.18 mmol, 3 eq)
was added followed by triethylsilyltrifluoromethanesulphonate (0.056 mL,
10 0.24 mmol, 4 eq). The reaction was stirred for 0.5 hr then poured into a 1:1
mixture of H₂O/saturated NaHCO₃ (1 mL) and extracted with CH₂Cl₂ (3 x
1 mL). The combined organics were dried (Na₂SO₄), filtered, and the
volatiles were removed. The residue was chromatographed with 1%
Et₂O/CH₂Cl₂ to give 35 mg of compound B (80% yield) as a clear glass. *m/z*:
15 720.5 (M+H)⁺.

C. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

20 To a solution of diethylzinc (0.24 mL of 1.0 M in heptane, 0.24
mmol, 5 eq) in 1,2-dichloroethane (1.5 mL) at -15 °C under argon was
added chloriodomethane (0.035 mL, 0.48 mmol, 10 eq), and the mixture
was stirred for 10 min. A solution of compound B (35 mg, 0.048 mmol) in
1,2-dichloroethane (0.40 mL) was slowly added, and the reaction mixture
25 was stirred for 1.5 hrs. The reaction was quenched by addition of
saturated NH₄Cl (1.5 mL) and extracted with CH₂Cl₂ (3 x 2 mL). The
combined organics were dried (Na₂SO₄), filtered, and the volatiles removed
in vacuo. To the residue was added 15% trifluoroacetic acid/CH₂Cl₂ (0.50

mL) and the reaction stirred for 15 min. The volatiles were removed under a stream of air and the residue was chromatographed with 70% EtOAc/hexanes to give 2.2 mg of title compound (10% yield- two steps) as a white film; m/z : 506.3 (M+H)⁺.

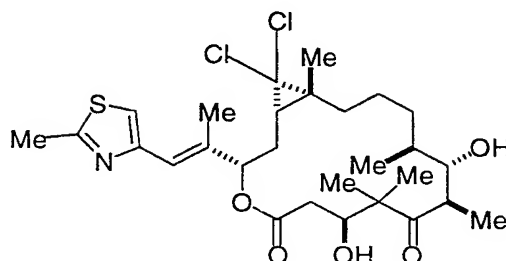
5 Alternatively, sodium hydroxide (0.3 ml of 50% solution in H₂O) was added to compound 1B (109 mg, 0.15 mmol), PhCH₂(CH₃CH₂)₃NCl (0.7 mg, 0.002 mmol), and EtOH (0.03ml) in CHBr₃ (1.0 ml). The resulting mixture was heated at 40°C for 2 hr. The brown reaction mixture was diluted with H₂O (30 ml), extracted with CH₂Cl₂ (3X30 ml), dried over Na₂SO₄,
10 concentrated and purified by flash chromatography (stepwise gradient: 5 to 25% Et₂O/hexanes) to afford a dibromocyclopropane intermediate as a light brown oil (40mg, 30% yield). (M+H)⁺ 892.3

 Bu₃SnH (3.4 mmol, 0.91 ml) was added to the dibromocyclopropane intermediate (0.34 mmol, 305 mg) and 2,2-azobisisobutyronitrile (0.034
15 mmol, 6 mg) in hexanes (7.0 ml). The reaction mixture was heated at 70 °C for 5 hr. The reaction was concentrated and purified by flash chromatography (stepwise gradient: hexanes to 20%Et₂O/hexanes) to afford a reduced cyclopropane intermediate as a clear film (228 mg, 91%). (M+H)⁺ 734.7.

20 The preceding cyclopropane intermediate(0.31 mmol, 228 mg) was dissolved in CF₃CO₂H/CH₂Cl₂ (20% solution by volume, 10 ml) and stirred at -15°C for 1.5 hr. The reaction mixture was concentrated and purified by flash chromatography (70%EtoAc/Hexanes) to afford the title compound as a clear oil (111 mg, 71%). (M+H)⁺ 506.3. ¹H NMR (CDCl₃, 400 MHz) δ
25 7.04 (s, 1H), 6.64 (s, 1H), 5.16 (dd, J=8.0, 3.4 Hz, 1H), 4.17 (dd, J=9.5, 2.8 Hz, 1H), 3.79-3.83 (m, 1H), 3.23 (dq, J=6.7, 4.5 Hz, 1H), 2.79 (s, 3H), 2.52 (dd, J=15.1, 9.7 Hz, 1H), 2.41 (dd, J=15.2, 2.9 Hz, 1H), 1.98-2.02 (m, 1H), 2.00 (s, 3H), 1.63-1.73 (m, 1H), 1.40-1.58 (m, 5H), 1.36 (s, 3H), 1.20-1.33

(m, 1H), 1.11-1.17 (m, 1H), 1.15 (d, J=6.8 Hz, 3H), 1.08 (s, 3H), 0.96 (d, J=7.0 Hz, 3H), 0.94 (s, 3H), 0.40-0.54 (m, 1H), 0.37 (dd, J=8.8, 4.1 Hz, 1H), -0.14-(-0.10) (m, 1H).

Example 2



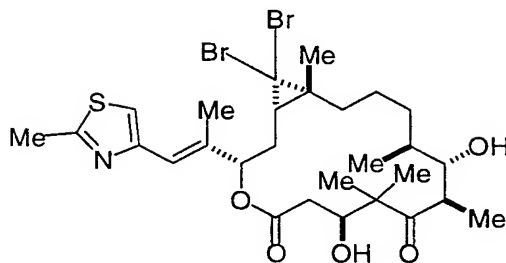
[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-bistriethylsilyloxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

Sodium hydroxide (1.7 ml of 50% solution in H₂O) was added to compound 1B (1.04 g, 1.44 mmol), benzyltriethylammonium chloride (7 mg, 0.03 mmol), and EtOH (0.06ml) in CHCl₃ (11 ml). The reaction mixture was stirred at room temperature for 2 hr. The brown reaction mixture was diluted with H₂O (60 ml), extracted with CH₂Cl₂ (3X50 ml), dried over Na₂SO₄, concentrated and purified by flash chromatography (stepwise gradient: hexanes to 8% EtOAc/hexanes) to afford compound A as light brown oil (361 mg, 31% yield). (M+H)⁺ 804.5

B. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

Compound A (0.27 mmol, 220 mg) in CF₃CO₂H/CH₂Cl₂ (20% solution by volume, 10 ml) was stirred at -15°C for 1.5 hr. The reaction was concentrated and purified by flash chromatography (70%EtOAc/Hexanes) to afford the title compound as a light brown oil (126 mg, 81%). (M+H)⁺ 574.4

Example 3

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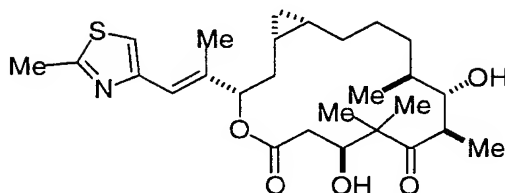
[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dibromo-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

- 10 **A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dibromo-7,11-bistriethylsilyloxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione**

Sodium hydroxide (0.3 ml of 50% solution in H₂O) was added to
 15 compound 1B (109 mg, 0.15 mmol), benzyltriethylammonium chloride (0.7 mg, 0.002 mmol), and EtOH (0.03ml) in CHBr₃ (1.0 ml). The resulting mixture was heated at 40°C for 2 hr. The brown reaction mixture was diluted with H₂O (30 ml), extracted with CH₂Cl₂ (3X30 ml), dried over Na₂SO₄. The organic extracts were concentrated and the residue was
 20 purified by flash chromatography (stepwise gradient: 5 to 25% Et₂O/hexanes) to afford compound A as light brown oil (40mg, 30% yield). (M+H)⁺ 892.3

- 25 **B. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dibromo-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione**

Compound A (0.0045 mmol, 4 mg) in CF₃CO₂H/CH₂Cl₂ (15% solution by volume, 10 ml) was stirred at -15°C for 1.5 hr. The reaction mixture was concentrated and purified by flash chromatography
 30 (70%EtoAc/Hexanes) to afford the title compound as a clear oil (2 mg, 66%). (M+H)⁺ 664.2

Example 4

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[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

- 10 A. **[4S-[4R*,7S*,8R*,9R*,16R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone C]**

To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis(cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with argon. The red suspension became dark, turning a homogeneous deep green after 1.5 hr with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 eq) was removed and cooled to -78 °C under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 eq). The reaction mixture was warmed to room temperature and stirred for 15 min. The volatiles were removed *in vacuo* and the residue was chromatographed two times on silica (25g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of compound A as a pale yellow viscous oil.

- 30 B. **[4S-[4R*,7S*,8R*,9R*,16R*(E)]]-4,8-Bis(t-butyldimethylsilyloxy)-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione**

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.43 mmol) was added to compound A (76 mg, 0.16 mmol) and 2,6-lutidine (0.074 mL, 0.64 mmol) in CH₂Cl₂ (2.5 mL). The reaction mixture was stirred at -20 °C for 30 min, and quenched with H₂O (10 mL). The reaction

mixture was extracted with CH₂Cl₂ (2X10 ml), dried over Na₂SO₄, concentrated and purified by flash chromatography (10% EtOAc/Hexanes) to afford compound B as a white solid (89mg, 79%). (M+H)⁺ 706.2

5 **C. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dibromo-7,11-bis(t-butyltrimethylsilyloxy)-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione**

10 To a solution of compound B (85 mg, 0.12 mmol) in CHBr₃ (1.0 ml) was added benzyltriethylammonium chloride (3.0 mg, 0.013 mmol), EtOH (0.010 mL), and then 50% NaOH (aq) (0.17 ml, 3.2 mmol). The reaction mixture was vigorously stirred at 50 °C for 48 hr, cooled to room temperature, and then chromatographed directly (7% EtOAc/hexanes) to give compound C (15 mg, 14%) as a pale yellow solid. (M+H)⁺ 878

15 **D. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Bis(t-butyltrimethylsilyloxy)-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione**

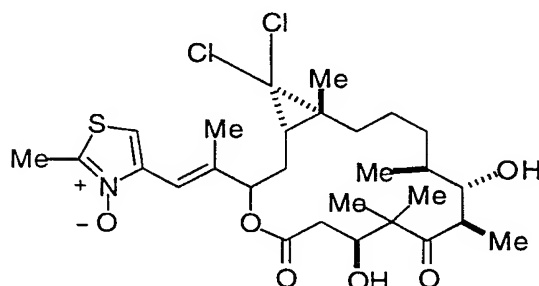
20 To a solution of compound C (11.5 mg, 0.013 mmol) in hexanes (0.20 ml) was added tributyltin hydride (0.021 ml, 0.080 mmol) followed by 2,2-azobisisobutyronitrile (0.0013 mmol, <1 mg). The reaction mixture was heated at reflux for 2 hr. The reaction mixture was cooled to room temperature. The volatiles removed under a stream of air, and the residue was chromatographed (0 to 8% EtOAc/hexanes) to give compound D (7.2 mg, 77%) as a clear oil. (M+H)⁺ 720

30 **E. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione**

35 To compound D (7.1 mg, 0.0099 mmol) at -15 °C was added 20% trifluoroacetic acid/CH₂Cl₂ (0.30 mL). The reaction was warmed to 0°C and stirred for 2 hr. The volatiles were removed under a stream of air, and the residue was chromatographed with 40% EtOAc/hexanes to give the title compound (4.3 mg, 89%) as a clear, viscous oil. (M+H)⁺ 492. ¹H NMR (CDCl₃, 400 MHz) 6.93 (s, 1H), 6.54 (s, 1H), 5.25 (dd, J=9.2, 3.6 Hz, 1H), 4.07-4.11 (m, 1H), 3.83-3.87 (m, 1H), 3.15-3.20 (m, 1H), 2.68 (s, 3H), 2.51

(dd, J=15.0, 9.2 Hz, 1H), 2.44 (dd, J=15.0, 3.4 Hz, 1H), 2.01-2.07 (m, 1H),
 2.03 (s, 3H), 1.67-1.71 (m, 1H), 1.44-1.53 (m, 3H), 1.37-1.45 (m, 1H), 1.34
 (s, 3H), 1.16-1.30 (m, 2H), 1.14 (d, J=7.0 Hz, 3H), 1.13 (s, 3H), 1.05-1.13
 (m, 1H), 0.97 (d, J=7.0 Hz, 3H), 0.57-0.72 (m, 3H), -0.33 (dd, J=9.7, 5.3 Hz,
 5 1H).

Example 5

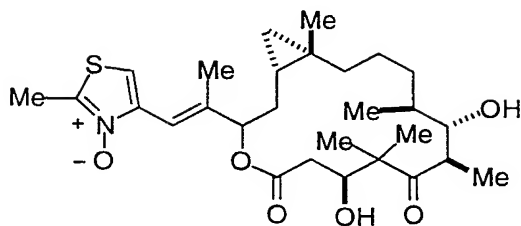


10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-3-oxo-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

15 m-Chloroperoxybenzoic acid (1.5 mmol, 260 mg) was added to compound 2B (303 mg, 0.53 mmol) in CH₂Cl₂ (12 ml). The reaction mixture was stirred at room temperature for 5 hr. The reaction mixture was washed with NaHCO₃ (2X50 ml), Na₂SO₃ (2X50 ml of 50mg/ml solution), H₂O (2X50 ml), and then dried over Na₂SO₄. The organic extracts
 20 were concentrated and the residue was purified using HPLC (500x30 mm YMC ODS column, 15 to 100% solvent B over 50 min; solvent A:10:90, H₂O:CH₃CN; solvent B: 90:10, H₂O:CH₃CN; flow rate: 20 ml/min) to afford title compound, as a white solid (91 mg, 27%). (M+H)⁺ 590.2

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Example 6

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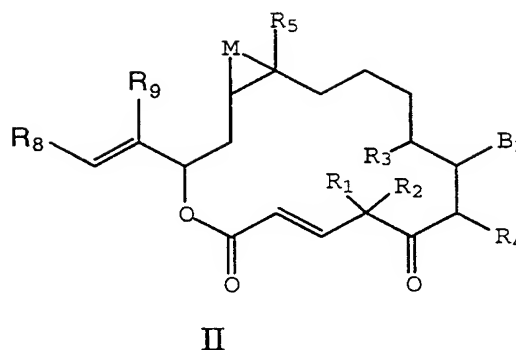
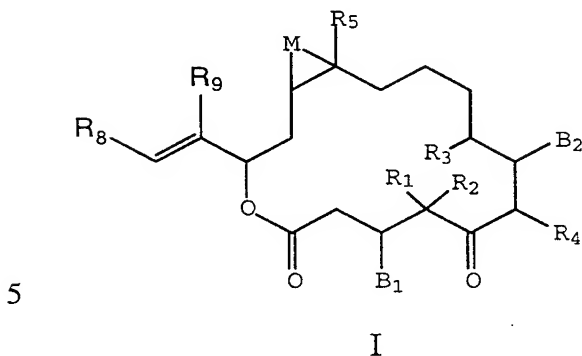
[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-3-oxo-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

m-Chloroperoxybenzoic acid (0.013 mmol, 2.2 mg) was added to compound 1C (3 mg, 0.006 mmol) in CH₂Cl₂ (0.15 ml). The reaction mixture was stirred at room temperature for 2.5 hr. The reaction mixture was concentrated and purified by flash chromatography (2%MeOH/CHCl₃) to afford the title compound (1.0 mg, 32%) as a white solid. (M+H)⁺ 522.3.

15

What is claimed.

1. A compound of the formula



B₁ and B₂ are selected from the group consisting of H, or OR₆;

R₁, R₂, R₃, and R₄, are selected from H, lower alkyl;

R₅ is selected from the group consisting of H, alkyl, substituted

10 alkyl;

R₈ is heterocyclo;

R₉ is hydrogen or lower alkyl;

R₆, is hydrogen or alkyl;

15 M is CR₁₀R₁₁.

R₁₀ and R₁₁ are selected from the group consisting of H, halogen,

alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo,

R₁₂C=O, R₁₃OC=O, R₁₄NHC=O, hydroxy, O-alkyl or O-substituted alkyl,

NR₁₅R₁₆;

20 R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₈ and R₁₉ are selected from the group

consisting of H, alkyl, substituted alkyl, aryl, acyl or substituted aryl.

R_{16} is selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{17}C=O$, $R_{18}OC=O$, $R_{19}SO_2$, hydroxy, O-alkyl, or O-substituted alkyl

and any salts, solvates or hydrates thereof.

5

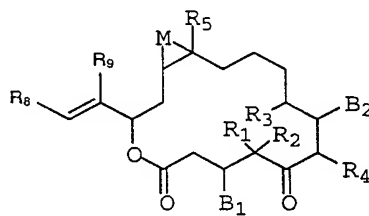
2. The compound of claim 1 wherein R_8 is a 2-methyl-4-thiazolyl.

3. The compound of claim 2 wherein R_{10} and R_{11} are halogen.

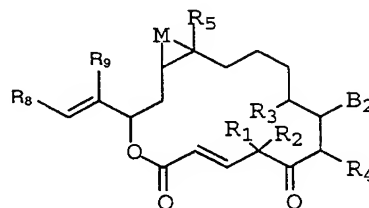
10 4. The compound of claim 3 wherein R_{10} and R_{11} are chlorine or bromine.

5. A compound of the formulas

15



I



II

Wherein

B_1 and B_2 are selected from the group consisting of H, or OR_6 ;

R_1 , R_2 , R_3 , and R_4 , are selected from H, lower alkyl;

20 R_5 is selected from the group consisting of H, alkyl, substituted alkyl;

R_8 is heterocyclo;

R_9 is hydrogen or lower alkyl;

R_6 is hydrogen or alkyl;

25

M is CH₂.

and any salts, solvates or hydrates thereof.

6. The compound of the formula [1S-
5 [1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione.
7. The compound of the formula [1S-
10 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione
8. The compound of the formula [1S-
15 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dibromo-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione
9. The compound of the formula
20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione
10. The compound of the formula
25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Dichloro-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-3-oxo-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione
11. The compound of the formula
30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16R*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-3-oxo-4-thiazolyl)ethenyl]-4-oxabicyclo[14.1.0]heptadecane-5,9-dione

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/07448

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 277/22, 313/00, 493/02

US CL :548/202; 549/270

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/202; 549/270

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Database Medline on STN, US National Library of Medicine, (Bethesda, MD, USA), AN 1998: 328821, NICOLAOU, et al. Synthesis and Biological Properties of C12, 13-Cyclopropyl-epothilone A and Related Epothilones. Chemistry and Biology. July 1998, Vol. 5, No. 7, page 365-372, see the attached.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 MAY 1999

Date of mailing of the international search report

03 JUN 1999

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